



The relationship of hypertrophic Cardiomyopathy and micro-rna's

Hipertrofik kardiyomiyopati ile Mikro-rnaların ilişkisi

Hypertrophic cardiomyopathy micro-rna

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Öz

Amaç: Hipertrofik Kardiyomiyopati (HKM miyokardiyal hipertrofiye neden olan primer kalp kası hastalığıdır. MikroRNA'lar (miRNA) proteinlerin sentezinin regülasyonunda rol alan hem hücre içinde hem de dolaşımda bulunabilen küçük RNA'lardır. Bu çalışma literatürde kardiyak hipertrofi ile ilişkili olduğu gösterilmiş 11 adet mikro-RNA'nın periferik kanda ekspresyon düzeylerine bakılarak HKM'ye özgü miRNA'lar olup olmadığını araştırmak amacıyla yapıldı. Gereç ve Yöntem: Çalışmaya mart 2012 ve mart 2013 tarihleri arasında kliniğimize başvuran Hipertrofik Kardiyomiyopati tanısı alan 26 hasta, hipertansif sol ventrikül hipertrofisi tanısı alan 25 hasta ile 24 kontrol kişisi alındı. Kan örnekleri alınıp 11 tane miRNA'nın ekspresyon seviyeleri RT-PCR yöntemiyle araştırıldı. miRNA ekspresyon seviyeleri 3 grup arasında karşılaştırıldı. Bulgular: Çalışmaya alınan gruplara arasında miR-1, miR-21, miR-22, miR-23a miR-29, miR-30, miR-34, miR-133 ve miR-199a ekspresyonu seviyeleri açısından gruplar arasında istatistiksel olarak anlamlı bir fark saptanmadı ($p>0,05$). Her üç grupta da miR-208 ve miR-290 ise ekspresyonu yetersiz olduğu için istatistiksel değerlendirmeye alınmadı. Tartışma: Çalışmaya alınan gruplara arasında miR-1, miR-21, miR-22, miR-23a miR-29, miR-30, miR-34, miR-133 ve miR-199a ekspresyonu seviyeleri açısından fark saptanmadı.

Anahtar Kelimeler

Hipertrofik Kardiyomiyopati; mikroRNA; Real Time PCR

Abstract

Aim: Hypertrophic cardiomyopathy (HCM) is a heart muscle disease which primarily causes myocardial hypertrophy. MicroRNAs(miRNA) are small RNAs which involved in the regulation of protein synthesis in the cell and circulation. In this study, 11 micro-RNAs shown in the literature to be associated with cardiac hypertrophy were investigated in peripheral blood by looking at the expression of miRNA level whether it is specific to hypertrophic cardiomyopathy or not. Material and Method: 26 patients with HCM, 25 patients with hypertension (HT) and 24 subjects of control group referred to our department between March 2012 and March 2013 were enrolled into this study. Blood samples were taken, and 11 miRNAs' expression levels were analyzed by the RT-PCR method. miRNA expression levels were compared between three groups. Results: miR-1, miR-21, miR-22, miR-23a miR-29, miR-30, miR-34, miR-133 and miR-199a expression levels were not different between groups ($p>0,05$). miR-208 and miR-290 levels have not been evaluated because of inadequate expression. Discussion: miR-1, miR-21, miR-22, miR-23a, miR-29, miR-30, miR-34, miR-133 and miR-199a expression levels did not show any difference in HCM, HT and control group.

Keywords

Hypertrophic Cardiomyopathy, Micro RNA, Real Time PCR

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Introduction

Hypertrophic cardiomyopathy (HCM) is a primary heart disease that usually develops without any other cardiac or systemic disease that causes hypertrophy and causes myocardial hypertrophy by retaining the interventricular septum of the undilated left ventricle [1]. Although HCM is seen in all ages, it most commonly occurs in ages 40-50. Annual mortality due to HCM is 1%, and the mortality rate is 2-4% in patients diagnosed under 14 years [2].

MicroRNAs (miRNAs) are small (18-25 nucleotides long), highly conserved, non-coding RNAs that can frequently be expressed in all species [3]. These RNAs act as endogenous repressors of the target genes by inhibiting translation and/or increasing messenger RNA (mRNA) degradation [4]. It has been shown that a single miRNA can affect hundreds of gene copies to govern complex expression of gene expression, thus causing general changes in the physiology of cells [5]. miRNAs are thought to play a key role in the cellular process in the pathophysiology of cardiovascular disease [6]. In various studies, changes in the spectrum of intracellular miRNAs have been reported to correlate with various cardiovascular events such as myocardial infarction, hypertrophy, cardiomyopathy, and arrhythmia [7]. In this study, it was aimed to investigate miRNAs, which are shown to be related to hypertrophy, in clinical and echocardiographical diagnosed patients with HCM and if the miRNA in patients with left ventricular hypertrophy due to hypertension is independent of hypertrophy or not.

Material and Method

The study was carried out at the Polyclinic of Department of Cardiology of Adnan Menderes University Faculty of Medicine between 22/03/2012 and 22/03/2013 after approval of the local ethics committee. Clinical and echocardiographic findings of HCM and hypertensive left ventricular hypertrophy were included among the patients admitted to the cardiology outpatient clinic. As a control group, non-hypertensive cases, and patients with no known HCM were included. Cardiovascular surgery (Coroner Artery Bypass Grafting, valve surgery), tumor history, chronic rheumatic disease, and elderly patients and cardiovascular causes enlarging the heart such as heart failure or advanced valve disease were the exclusion criteria. Hypertrophic cardiomyopathy patients (n = 26 / Group 1), hypertensive left ventricular hypertrophy patients (n= 25 /Group 2) and control group (n=24 /Group 3) were included in the study.

Echocardiographic evaluation was performed with Hewlett Packard Sonos 5500 instrument (2.5 MHz probe) in accordance with the American Heart Association and the European Cardiology Association Heart Cavity Measurement Guide [8]. Measurements were obtained from the parasternal long and short axis in the left side position and apical two and four space images. Left ventricular systolic function was evaluated by ejection fraction (modified "Simpson" method) and fractional shortening.

Diagnostic criterion for HCM was, the presence of hypertrophic (wall thickness ≥ 15 mm) but not dilated left ventricle assessed with 2-dimensional echocardiography after excluding pathologies such as hypertension, aortic stenosis, subvalvular membrane and systemic disease which could cause left ventricular hypertrophy. Asymmetric septal hypertrophy was assessed as

having a septum wall thickness ≥ 1.3 [9]. Continuous (CW) Doppler echocardiography at rest and LVOT gradient ≥ 30 mmHg were accepted as obstructive HCM.

Again, hypertensive left ventricular hypertrophy diagnosis was defined as having a septum and/or posterior wall thickness of ≥ 1.1 cm with a history of hypertension. Left ventricular mass was calculated as $(0.8 \times 1.04 \times ((LVED + pw + ivs)^3 - (LVED)^3) + 0.6$ according to the Devereux formula and the left ventricular mass index was calculated by dividing this value by body surface area. Left ventricular mass index > 100 gr / m² in women and > 125 gr / m² in men was considered to be left ventricle hypertrophy [10].

The presence of systolic forward movement (SAM) was evaluated by 2-dimensional echocardiography on transthoracic parasternal long axis and apical 4-chamber sections [11]. The LVOT gradient was assessed by placing continuous Doppler on the left ventricular outflow tract. Peak and mean pressure gradients were recorded.

Collection and Preservation of Blood Samples

Peripheral venous blood of all cases was collected and centrifuged with miRNA-specific EDTA tubes and stored at -80°C .

miRNA Expression Analysis

For isolation of total RNA containing miRNAs, the miRNeasy Kit (Qiagen), which can purify all RNA over 18 nucleotides, was used. Mi-RNA samples were transformed into cDNA using the reverse transcriptase enzyme and then inserted into the real-time PCR reaction to study 11 miRNA levels, miR-1, miR-21, miR-22, miR-23a, miR-29, miR-30, miR-34, miR-133, miR-199a, miR-208 and miR-290. In the study, the microRNA reference gene (housekeeping gene) SNOR48 was used and those with a Ct (cycle of threshold) value greater than 40 were not studied.

Data Analysis

Analysis of the data was performed using a computer program called "Light Cycler® 480 Quantification Software" using the $\Delta\Delta\text{CT}$ method. For further data analysis, the GenEx qPCR analysis software (www.exiqon.com/mirna-pcranalysis) of the used kits company was used.

Statistical Analysis

Statistical analyses were performed using the SPSS for Windows version 15 package program, and $p \leq 0.05$ was considered statistically significant.

The normal distribution of the quantitative data was evaluated by the Kolmogorov-Smirnov test. The normal variance was analyzed by one-way analysis of variance between groups, and descriptive statistics were presented as the mean \pm standard deviation. Comparison of normal non-dispersive quantitative data between groups was analyzed by Kruskal Wallis analysis of variance, and descriptive statistics were presented in median (25-75 percentile) format. Spearman Correlation test or Pearson correlation test was used to examine the relationship between LV MASS and LVMASS index values according to the normal distribution of variables. Chi-square analysis was used to compare qualitative data, and descriptive statistics were

shown in frequency (percentage).

Results

Gender distribution of 26 HCM patients, 25 hypertensive patients and 24 control subjects were found to be female/male 42.3% / 57.7%, 60% / 40% and 54.2% / 45%, respectively and there was no statistically significant difference between groups in terms of gender distributions (p = 0.435). There was no statistically significant difference between the groups in terms of age, height, and weight (p = 0,093, p = 0,441, p = 0,128, respectively). The age range of all cases was determined as 20-65. There was no difference in smoking, alcohol, coronary artery disease, and diabetes mellitus when the background of the groups was examined. The HCM group was more likely to use the beta blockers (BB) (p: 0,00012). In hypertensive patients group, more frequent calcium channel blockers (CCB) (p: 0,0001), diuretic (p: 0,001), angiotensin converting enzyme inhibitor (ACEi) (p: 0.046), angiotensin receptor blocker (pB) (p. 0.01) and statin use was detected (p: 0.013). The incidence of anti-thrombocyte usage was higher in patients with HCM group than other groups (p: 0.035) (Table 1).

Table 1. Drug use and risk factors of the cases

	Control (n=24)	Hypertension (n=25)	HCM (n=26)	P
Gender	13/11	15/10	11/15	0,435
Female/Male	(54,2/45,8%)	(60/40%)	(42,3/57,7%)	
Age	46,88±7,708	53,48±10,304	52,23±12,539	0,093
Height	165,63 ±7,649	167,0±5,508	167,92±5,713	0,441
Weight	78,9±15,966	82,7±16,108	83,2±14,877	0,128
History of DM	5 (20,8%)	7 (28%)	3 (11,5%)	0,337
History of CAD	2 (8,3%)	3 (12%)	1 (3,8%)	0,561
BB drug	0	13 (52%)	19 (73,1%)	0,00012
ACE inhibitor	1 (4,2%)	8 (32%)	6 (23,1%)	0,046
ARB	1 (4,2%)	12(48%)	4 (15,4%)	0,01
CCB	0	13 (52%)	6 (23,1%)	0,0001
Diuretics	0	11(44%)	7 (26,9%)	0,001
Antithrombotic drugs	3 (12,5%)	8 (32%)	12 (46,2%)	0,035
Statins	1 (4,2%)	7 (28%)	1 (3,8%)	0,013

Abbreviations: DM: Diabetes Mellitus, CAD: Coronary artery disease, BB: Beta blocker, ACE inhibitor: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, KKB: Calcium chanel blocker,

A total of 26 HCM patients were included in the study. Of these, 19 were septal type HCM, 3 were apical HCM, and 4 were concentric HCM patients. SAM was detected in 11 (42.3%) of HCM patients, and the gradient was found in LVOT in 14 (53.8%). Of the HCM patients, 22 had sinus rhythm, and 4 had AF. 50% of HCM patients had a familial transition story. In 4 of the HCM cases (15.4%), there was a history of syncope/VT/arrest. Among the miRNAs studied (miRNA-1, miRNA-21, miRNA-22, miRNA-23a, miRNA29, miRNA30, miRNA-34, miRNA133, miRNA199a, miRNA208, miRNA290), the expression of miRNA 208 and miRNA 290 was not statistically evaluated because it was inadequate between the groups. There was no statistically significant difference in the expression of miRNAs between the groups (Table 2).

Table 2. miRNA Expression Values of cases

miRNA	Group	Mean ± SS	Min-Max	p
miRNA-1	Control (n=24)	0,00469 ± 0,0083	0,00005 - 0,0318	0,594
	Hypertension (n=25)	0,00251 ± 0,00185	0,00015 - 0,00754	
	HCM (n=26)	0,00318 ± 0,00514	0,00031 - 0,0178	
miRNA-21	Control (n=24)	3,676 ± 7,645	0,0384 - 38,06	0,858
	Hypertension (n=25)	2,636 ± 3,928	0,00003 - 14,68	
	HCM (n=26)	2,886 ± 7,812	0,00103 - 40,48	
miRNA-22	Control (n=24)	0,482 ± 0,993	0,00561 - 4,924	0,989
	Hypertension (n=25)	0,447 ± 0,629	0,00025 - 2,764	
	HCM (n=26)	0,456 ± 0,885	0,0219 - 3,977	
miRNA-23	Control (n=24)	0,605 ± 1,618	0,00139 - 7,792	0,617
	Hypertension (n=25)	0,542 ± 1,175	0,0215 - 5,84	
	HCM (n=26)	0,293 ± 0,449	0,00375 - 1,681	
miRNA-29	Control (n=24)	0,069 ± 0,176	0,00233 - 0,8763	0,741
	Hypertension (n=25)	0,0927 ± 0,184	0,00143 - 0,9063	
	HCM (n=26)	0,0558 ± 0,13	0,00372 - 0,6474	
miRNA-30	Control (n=24)	0,0117 ± 0,037	0,00018 - 0,1697	0,618
	Hypertension (n=25)	0,019 ± 0,049	0,00038 - 0,2124	
	HCM (n=26)	0,007± 0,00932	0,00036 - 0,0296	
miRNA-34	Control (n=24)	0,0205 ± 0,068	0,00057 - 0,3	0,319
	Hypertension (n=25)	0,00403± 0,00275	0,00037 - 0,00962	
	HCM (n=26)	0,00544 ± 0,00378	0,00151 - 0,0154	
miRNA-133	Control (n=24)	0,00209 ± 0,00235	0,00023 - 0,00725	0,596
	Hypertension (n=25)	0,00692 ± 0,026	0,00033 - 0,121	
	HCM (n=26)	0,00299 ± 0,00396	0,00025 - 0,0144	
miRNA-199	Control (n=24)	0,072 ± 0,25	0,00148 - 1,167	0,341
	Hypertension (n=25)	0,0179 ± 0,027	0,00011 - 0,1278	
	HCM (n=26)	0,0168 ± 0,0322	0,00101 - 0,1618	

HCM, hypertension, and control groups were evaluated for the left ventricular mass index (LV MASS index) and miRNA correlation. Among all subjects; the minimum value of LV MASS index was 53 g/m2, maximum value was 335 g/m2 (mean value=131,26 g/m2, n=75). There was no relationship between miRNA expression and LV MASS index among the groups (Table 3).

Discussion

MicroRNAs are small RNA molecules, about 18-25 nucleotides in length, that are encoded in high conserved DNA regions but not in protein translation. miRNA was first discovered in 1993 by Lee et al. in the Victor Ambors lab. In 2001, the miRNA name was started to be used [24]. miRNAs have been identified in a large number of organisms, and around 1500 are found in humans. More than 60% of protein synthesis is thought to be regulated by miRNAs in humans, so the possibility that microRNAs may play a role in the development of diseases is gaining strength. The demonstration that microRNAs are present in peripheral blood and other body fluids suggests that they can be used as markers in the diagnosis and

Table 3. Relation of LV MASS and miRNA with HCM, hypertension and control groups

		LVMASINDEX
miRNA-1	r	-.019
	p	,904
	n	42
miRNA-21	r	-.091
	p	,444
	n	73
miRNA-22	r	-.004
	p	,973
	n	73
miRNA-23	r	-.158
	p	,189
	n	71
miRNA-29	r	-.041
	p	,736
	n	71
miRNA-30	r	,087
	p	,525
	n	56
miRNA-34	r	,091
	p	,484
	n	62
miRNA-133	r	,199
	p	,138
	n	57
miRNA-199	r	-.200
	p	,096
	n	70
miRNA-208	r	,510
	p	,090
	n	12
miRNA-290	r	-.200
	p	,800
	n	4

follow-up of diseases [13].

In this study, we examined the expression of microRNAs that are associated with cardiac hypertrophy by real PCR method and examined whether they are hypertrophic cardiomyopathies specific microRNAs. There was no statistically significant difference between the expression of miRNAs regarding HCM, hypertension and control group and the LV MASS index regarding miRNA expression.

In the study of Roncarati et al., MiR-27a, miR-199a-5p, miR-26a, miR-145, miR-133a, miR-143, miR-199a-3p, miR-155, miR-30a, and miR-21 were significantly associated with cardiac hypertrophy and increased in plasma of patients with HCM. However, it was observed that miR-199a-5p, miR-27a, and miR-29a are correlated with hypertrophy, and only miR-29a is correlated with fibrosis [14].

miRNA-1 is a micro-RNA that is most abundant in the heart and is specific for muscle tissue and plays an important role in cardiac development and differentiation. Also, miRNA-1 controls

cardiac hypertrophy through calcium-dependent signaling. Li and colleagues have shown that miRNA-1 reduces cell surface area by inhibiting TWF-1 protein and also inhibiting miRNA-1's effect, leads hypertrophy [15].

Another study by Sayed et al. in rats examined microRNA expression during cardiac hypertrophy. Rats were subjected to hypertrophy of the left ventricle with aortic banding, and in comparison with control group rats, the decrease in miRNA-1 expression of left ventricular hypertrophic rats was found [16]. Care and colleagues have shown that the expression of mi-RNA-1 decreases in hypertrophic cardiac myositis [17]. Although our study has no significance (p: 0,594), the fact that the control levels of miRNA-1 are greater than hypertension and HCM group supports these studies.

Endogenous inhibition of miR-21 or miR-18b increases hypertrophic growth [18]. Patrick and colleagues studied the effect of miR-21 on the pathologic cardiac remodeling by creating stress on the heart with aortic ligation, calcineurin, angiotensin and MI model between normal mice and mice with deleting miR-21 mutation. There was no significant difference in hypertrophy, cardiac remodeling, MI scar tissue among the two groups but it was observed that miR-21 was markedly upregulated in response to all stress factors in the non-mutant group of mice. Even, an increase in the ratio of heart tissue to total body weight was found in mutant rats. In the same study, untreated mice were compared with mice given anti-miR-21 and the increase in miR-21 induced by aortic banding and angiotensin II-stimulated miR-21 increase was effectively inhibited by anti-miR-21 but not in the control group. There was no difference in phenotype, cardiac function, myosin heavy chain, and cardiac remodeling in these groups [19]. In our study, no significant difference was observed regarding miR-21 expression among the groups, but the values of the control group were higher than those of HT and HCM group (p: 0,858). This information appears to be in contradiction to Patrick et al.'s study, although it is partially in agreement with the knowledge that miR-21 is not effective in cardiac hypertrophy and remodeling and that counter-compensatory mechanisms are effective. We think that miRNA-21 may behave differently in different species when it is thought that the work is performed in mice.

Studies have shown that miR-22 is a tumor suppressor and increases apoptosis by inducing senescence in cancerous cells [20]. In a study by Huang et al., it has been shown that cardiac hypertrophy stimulating agents, such as phenylephrine, decrease this effect after miR-22 inhibition. Later, agents that mimic the miR-22 effect were found to increase cell surface area when injected into cardiomyocytes, and in these rats, genes that were normally active in fetal life such as ANP, BNP, α -actin, and β -MHC were observed to reactivate. When inhibited miR-22 mutant mice compared to control mice, it was found that ISO significantly reduced induced cardiac hypertrophy in mutant mice. Furthermore, the functional loss of miR-22 accelerated fibrosis in mutant mice thus leading to both decreased systolic function and dilated cardiomyopathy [21]. In our study, no statistically significant difference was found between the groups at the expression level of miR-22, and the values were very close to each other. When the groups were analyzed regarding LV mass index, no statistically significant difference was found

($p: 0,989$). We think that this is because miRNA-22 is different in humans regarding its target and its action mechanism. The fact that some target genes have been identified, such as sirtuin 1 (sirt-1) and human histone deacetylase (HDAC4) for miR-22 in situ, support this idea [22].

MicroRNA-199 is another micro-RNA that has been shown to be associated with cardiac development and hypertrophy. In a study by Song et al. In rats with aortic hypertrophy, inhibition of miR-199a has been shown to reduce hypertrophy in cardiomyocytes [23]. Another study of late-onset cardiomyopathic patients has shown that expression of miR-199a is downregulated, which has been shown to activate intracellular proteases leading to cardiac mass loss during cardiac dilation [24]. In our study, although there was a statistical difference in cardiac hypertrophy between the groups, there was no statistically significant difference in terms of miR-199a expression ($p: 0,341$). However, the values of the control group are higher than those of the hypertension group, and the values of the hypertension group are higher than those of the HCM group. This finding is in contradiction with the literature.

Restrictive factors for our study include the collection of cases from a single center, a small number of hypertension cases, HCM and control group patients. Our study being carried in peripheral blood while most of the other studies are carried out in animal models, lack of human studies on the subject and using real time PCR method as well as molecular research techniques such as microarray, northern blot, western blot, or cell culture as a method, and looking at many miRNA values are the limiting points of study. No follow up done for arrhythmia attack or sudden death to compare miRNA values for patient prognosis is another limitation. Although there is no significant difference in gene polymorphism between the patient groups and the control group, it is considered that the mean and standard deviation values of the miRNAs of each group are different from each other, so that the significance can be obtained in studies where more patient participation is achieved.

Conclusion

In this study, we investigated the levels of miRNAs in HCM and hypertensive patients and tried to reveal the relation with diseases. As a result; There was no significant difference between miRNA gene polymorphism and disease, no significant difference between gene polymorphism and male and female sex, and there was no significant correlation between miRNA and LV Index. There is a need to study with more patients to reveal miRNA gene polymorphisms association with cardiac pathologies.

It is clear that miRNA takes an active role in the development of cardiac pathology. The participation of larger patient groups and/or more animal studies will increase knowledge in this regard. It is also believed that the understanding of the role of miRNA in the pathogenesis of cardiac pathologies may be illuminated by cardiac tissue samples taken from humans.

Animal and Human Rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the

1964 Helsinki Declaration and its later amendments or comparable ethical standards

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

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Conflict of interest

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